



PATENT
MSB-7267

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

W. Wang
R. Nayar
M. Shearer

Serial No.: 09/605,577

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Title: Stabilized Interleukin 2

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 CFR
1.132

EXAMINER: J. Seharaseyon

ART UNIT: 1647

Sir:

I, Wei Wang, declare as follows:

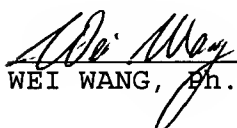
1. I am a co-inventor in the above-identified application and have been awarded a Ph.D. degree in Pharmaceutical Sciences from the University of Southern California. I have approximately 10 years experience in the preparation and/or characterization of therapeutic proteins.

2. I have been advised that the examiner responsible for the above-identified application has raised the question as to whether the application as filed is enabling for all interleukin 2 and all muteins of interleukin 2.

3. As shown in the examples of the application, the use of histidine contributed significantly to the stability of the mutein identified as N88R.

4. In addition, as shown in the attached graphs, the use of histidine for the stabilization of a naturally occurring human interleukin 2 (wild-typed) is equally effective. See the enclosed charts showing aggregation and recovery data obtained when histidine was used in both wild typed and N88R interleukin 2 studies.

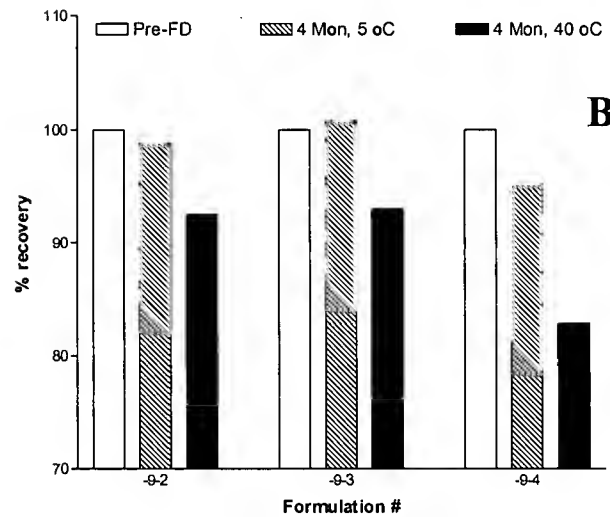
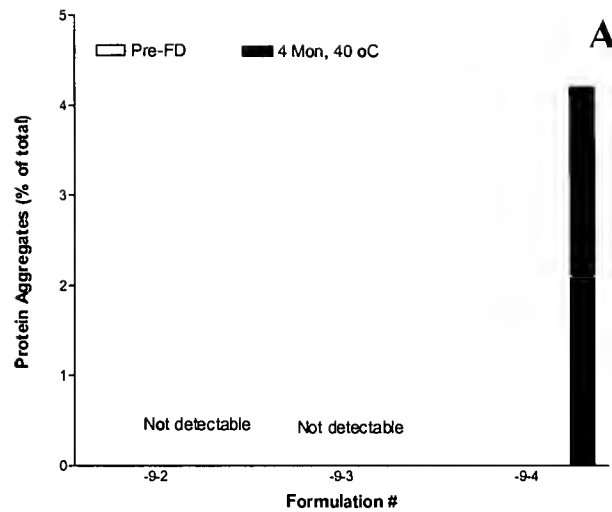
The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the instant patent application or any patent issuing thereon.



WEI WANG, Ph.D.

1/24/2001

Date



Stability of N88R IL-2 and wild-type IL-2 during storage of lyophilized formulations.

Figure A shows the formation of protein aggregates as monitored by SEC-HPLC after storage of the lyophilized formulations at 40 °C for 4 months.

Figure B is the protein recovery (of initial) as monitored by RP-HPLC after storage of the lyophilized formulations at both 5 and 40 °C for 4 months. The three formulations have the following compositions:

- 9-2: 1 mg/mL N88R IL-2, 2% glycine, 1% sucrose, and 20 mM histidine at pH 5.5.
- 9-3: 1 mg/mL **wild-type IL-2**, 2% glycine, 1% sucrose, and 20 mM histidine at pH 5.5.
- 9-4: 1 mg/mL N88R IL-2, 2% glycine, 1% sucrose, and 20 mM **citrate** at pH 5.5.